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Experience of Hyperbaric Oxygen Treatment on a Patient with Acute Ischemic Locked-in Syndrome

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The characteristics of locked-in syndrome (LIS) are quadriplegia and anarthria with preservation consciousness. It is difficult to manage these symptoms. There have been several reports revealing the significant effectiveness of hyperbaric oxygen (HBO_2) therapy on acute stroke, however, some journals show less favorable results using this treatment. There has also been no definite reporting of which lesions of the stroke are suitable for HBO_2 therapy. We present a 65-year-old woman, suffered from acute ventral pontine infarction with LIS. Two days after onset, she received HBO_2 therapy. One month later, she showed obvious functional recovery. There has been no previous published report discussing HBO_2 therapy for acute ischemic pontine infarction. This is the first report regarding the obvious improvements of LIS using HBO_2 therapy. Consequently, these findings suggest that HBO_2 therapy could be used in conjunction with physical and rehabilitative therapy in the treatment of acute LIS for maximal functional improvement.

Key words: hyperbaric oxygen therapy, locked-in syndrome, stroke, function

INTRODUCTION

Locked-in syndrome (LIS) is characterized by quadriplegia, lower cranial nerve palsies, anarthria, with preservation of vertical gaze and consciousness.[1] It is associated with lesions of the brainstem, usually at the level of the ventral pons.[2] The most common cause is vascular-related, usually due to ischemia from basilar artery occlusion or from pontine hemorrhage.[2] The prognosis for LIS is usually extremely poor.[2] In patients with LIS from vascular causes, the mortality rate is as high as 67% and the recovery rate is only 10% (those achieving independence in activities of daily living) and many that remain locked-in have also been reported.[2] Outcome has been reported to be better in ischemic LIS patients who undergo thrombolysis within 6 hours of onset.[3] But it is usually difficult to start thrombolysis within 6 hours due to the time to the hospital and the efficacy of diagnosis. Normally, the patient only undergoes intensive stroke management protocols and antiplatelet therapy. Do we have another adjective treatment for these types of patients? The efficacy of hyperbaric oxygen (HBO_2) therapy has been proven for many years since Ingvar and Lassen first advocated it as an adjunct in the treatment of ischemic stroke because of the ability of this therapy to deliver a greatly increased partial pressure of oxygen to the tissues.[4]

HBO_2 therapy is the therapeutic administration of 100% oxygen at pressure >1 atmosphere absolute (ATA).[5] Typically, treatments involve pressurization between 2 and 3 ATA for periods between 60 and 120 minutes daily.[5] The potential benefits of HBO_2 therapy have been demonstrated successfully in some animal studies.[6,7] There have also been several cases of ischemic strokes in humans treated with HBO_2, claiming improvement on clinical or experimental foundations.[4,8,9] Even with successful cases as mentioned previously, there has been no definite report to suggest lesion sites of the stroke suitable for HBO_2. There is also no study presenting LIS treated with HBO_2 therapy. We conducted a case of acute infarction of the pons with LIS to assess the efficacy of HBO_2.

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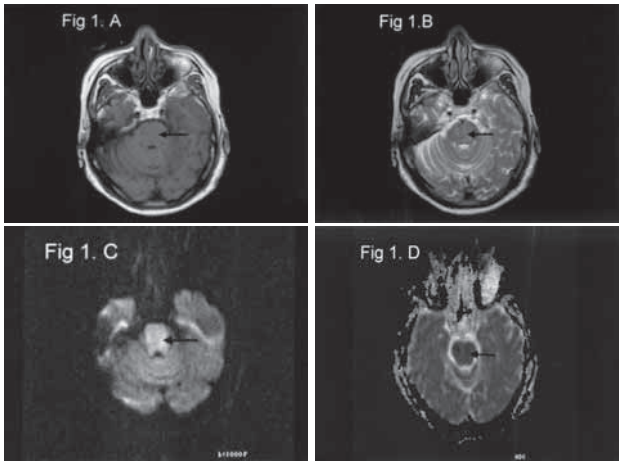

Fig. 1 (A): T1-weighted magnetic resonance imaging with an arrow pointing to the iso to hypo intensity area in the most of pons. (B): T2-weighted magnetic resonance imaging with an arrow pointing to the iso to hyper intensity area in the most of pons. (C): Diffusion-weighted (DWI) magnetic resonance imaging with an arrow pointing to increase signal in the most parts of pons. (D): Apparent diffusion coefficient (ADC) magnetic resonance imaging with an arrow pointing to decrease signal in the most parts of pons.

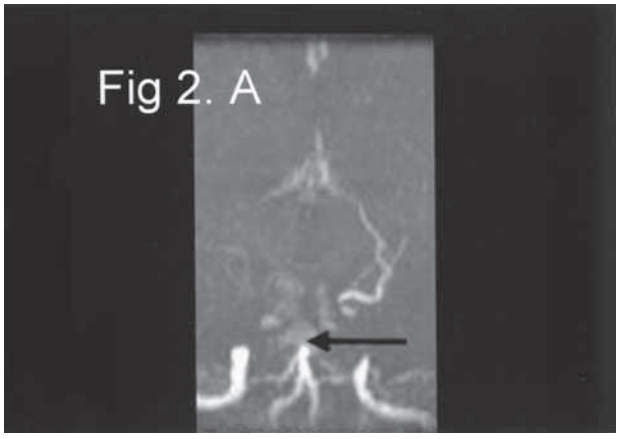

Fig. 2 A: Magnetic resonance angiography (MRA) with an arrow pointing to total occlusion of the middle and distal thirds of basilar artery

CASE REPORT

A 65-year-old woman suddenly suffered from weakness of the left limbs and slurred speech. Initially, she was sent to a local hospital for help, where brain CT revealed no significant abnormality. At that time, she was conscious and alert, and muscle power of left limbs was grade 4-5. One day later, deterioration of consciousness with quadriplegia and difficulty swallowing were found. Due to the worsening of the symptoms and limitations of the local facility/faculty, she was sent to our hospital. Upon arrival at our hospital, where axamination revealed quadriplegia, facial weakness, hyperreflexia of the arms and legs, bilateral Babinski's response, and dysphagia. Lateral gaze was limited, but preserved consciousness and vertical eye movement. She could communicate us with eye blinks and vertical eye movements. Sensation was tested by yes-no questions via eye blinks, revealed intact. Magnetic resonance image (MRI) of the brain showed no significant finding on T1,T2-weighted images(Figure 1,A, B), howerver acute infarctions of the most areas of the pons was presented on diffusion-weighted image (DWI) (Figure 1, C) and apparent diffusion coefficient (ADC) (Figure 1, D). Magnetic resonance angiography (MRA) (Figure 2, A) revealed total occlusion of the middle and distal thirds of basilar artery. She did not receive thrombolytics at that time because the symptoms maintained for more than 24 hours and there was the risk of compression of the brain stem by hematoma. She had a history of hypertension, with regular medication for 20 years. She also had a history of hyperlipidemia and type 2 diabetes mellitus without good control for 2 years. She was also a victim of hyperurecemia. She had no history of smoking. There was no specific illness in her family background.

The chest x-ray films revealed cardiomegaly, tortuosity of the aorta with atherosclerotic calcifications and increased bilateral pulmonary interstitial markings. The patient had a glucose (fasting) of 375 mg/dL (normal: 70-105 mg/dL), total cholesterol of 286 mg/dL (normal: 0-200 mg/dL), triglyceride of 474 mg/dL (normal: 0-200 mg/dL), uric acid of 7.5 mg/dL (normal: 2.4-7 mg/dL), ALT of 51 U/L (normal: 0-31 U/L), neutrophil of 78.6% (normal: 40-74 %), lymphocyte of 15.4 % (normal: 19-48 %), C-reactive protein of 0.72 mg/dL (normal: 0-0.5 mg/dL). The laboratory tests, which included blood urea nitrogen, creatine, alkaline phosphatase, AST, sodium, potassium, total calcium, and inorganic phosphorus, all had results within normal limits.

She was then admitted to our ICU for further evaluation and management. During the ICU period, coma was presented and needed ventilator support, The symptoms persisted for 2 days,. After the possibility of HBO_2 therapy was explained to her family by a medical doctor, this patient started to undergo 60–minute HBO_2 treatments

at 2 ATA in a monoplace HBO_2 chamber (Sechrist Industries, model 2800), 5 times per week, for a period of 20 times. After 1 month, she reached some level of functional recovery in several areas.

RESULTS

With respect to communication, she couldn't speak in complete sentences, but uttered single words consistently. She showed improvement from no function of the mouth to being primarily fed by mouth. Light reflex, oculocephalic reflex, gag reflex and corneal reflex were improved from uncertain to significant present, which means brain stem functions were improved. Coma scale was improved from 2T to 15. Maximum inspiratory pressure was improved from 20.0 cm H_2O when need ventilator support to 115 cm H_2O without any oxygen therapy. Nothing was more noticeable than improvements to mobility, as she recovered dramatically from quadriplegia to hemiparesis in the left side, which means muscle power was improved from zero in four limbs to 3 in the left side and 4-5 in the right side. Furthermore she could sit in a wheelchair manually being pushed. Her motor function reached moderate recovery, according to the Patterson and Grabois classification,[2] which defines a patient achieving moderate motor return with independence in some, but not all ADLs.

Barthel Index improved from 0 to 45. Modified Rankin Scale improved to 4, which defines moderately severe disability as the inability to walk and to attend to one's own bodily needs without assistance. The National Institutes Health Stroke Scale showed improvement from 32 to 6.

DISCUSSION

Although spontaneous recovery could not be excluded, we have a number of reasons to support the HBO_2 effect as our patient had some characteristics that obstructed spontaneous recovery. First, the patient is a ventral pontine infarction case, and some literature has shown that the prognosis and mortality rate of vascular group of LIS is worse than the nonvascular group.[2] Second, earlier rehabilitation and more effective nursing care can remarkably reduce mortality rate in acute LIS.[10, 11] Un-fortunately, our patient did not undergo early aggressive rehabilitation treatment. She just underwent 20 HBO_2 treatments and received basic nursing and rehabilitative care which included positioning (lying prone and supine) in bed, postural drainage and elevation to prevent edema of paralyzed hands and feet, aspiration of bronchial secretions. Another reason was that under general conditions, the functional recovery of this type of patients is significantly improved after 4 months of onset.[10] However, the recovery of our patient occurred quite obviously within one month. This evidence lends itself to support the effectiveness of HBO_2 for this patient, although spontaneous recovery may also be attributed to this outcome.

Before introducing the effectiveness of HBO_2, we should understand the mechanisms of brain ischemia. Brain ischemia can cause brain tissue injury in the ischemic stage and reperfusion stage. In the ischemic stage, the neuron used anaerobic pathway, cause proteolysis, membrane damage, and even cell death due to acidosis from lactate accumulation.[12] It also causes glutamate to be over-released and glutamate receptors to be overactive, which cause neurological excitotoxic damage.[13] In the reperfusion stage, the inflammatory mediators, endogenous substrate, and reactive oxygen species can cause ischemia reperfusion(I/R) injury.[14]

The important mechanism of HBO_2 is its high oxygen pressure. In hypoxia, cerebral blood flow is not enough to maintain neuronal function, but sufficient perfusion pressure can.[8] The optimal oxygen pressure for treating head injury is 1.5 ATA.[15] Above this pressure, there is a sufficient increase in the arterial PO_2, so that even minimal blood flow perfusion is apparent in the penumbral areas at a sufficiently high pressure. Meanwhile, raising the tension of available oxygen can increase the driving force and reduce the barriers of diffusion.[16]

HBO_2 effect on brain ischemia had been reported in many animal and human studies. In the animal studies, the treatment effect could be from enhancing oxygen to marginally pneumbra,[6,7] reduction of cerebral edema, decreasing lipid peroxidation, and restoration of the functional blood-brain barrier.[17] HBO_2 treatment may also provide a beneficial effect for I/R injury due to the inhibition of leukocyte activation.[18]

In humans, the positive effects were shown on an HBO_2 group in a double-blind study.[19] Another study showed the dose/effect of HBO_2 treatment, which revealed the higher values of clinical neurologic status improved, the greater dose, which was calculated considering the ATA, the duration of a single HBO_2 exposure (hours), and the number of HBO_2 treatments given.[20] Meanwhile, some double-blind prospective protocols showed no significant findings between control and HBO_2 groups.[7, 21,22] According to the above studies, HBO_2 treatment in humans was less effective than animal studies. This conclusion could be

due to small sample sizes,[5] the stage of patients enrolled (acute, subacute, or chronic), the documentation of the type and severity of stroke, and the dosage of hyperbaric oxygen therapy given varied.[22] Therefore, to determine how effective HBO_2 treatment is in patients with stroke still requires significant study.

There is no definite report that reveals which lesion sites of the stroke were suitable for HBO_2 treatment. We have some reasons to consider the autoregulation and collateral flows of vertebrobasilar artery(VBA) system were better than the internal carotid artery system. First, a report revealed autoregulation and collateral flows of vertebral artery were better than that of internal carotid artery during hypotension.[23] Second, a literature reviewed 100 cases and showed that vertebral artery ligation was far less harmful than carotid artery ligation.[24] Another report showed the same result, which revealed the symptoms were not manifested after temporary vertebral artery ligation.[25] Third, a literature reported a patient of air embolism within basilar artery due to accidentally be injected with air was successfully treated by HBO_2.[26] The patient underwent 2.5 ATA for 90 minutes everyday. The symptoms and signs resolved completely within one week.[26] These findings suggest that vertebrobasilar artery system receives good collateral flows and maintain excellent autoregulation. The effect of HBO_2 depends on oxygen pressure and appropriate blood flow. The areas with better autoregulation and collateral flows will have more blood flow to carry oxygen to penumbral areas during brain infarction. Therefore, this will enhance the effect of HBO_2. Meanwhile, there were more survival brain cells in the areas with better collateral flows. This offered a good chance for HBO_2 to intervention. This means that overall the efficacy of HBO may be better in the areas which VBA system inervated when ischemic infarction occurs. These may explain why LIS treated with HBO_2 could provide more obvious improvements in our case. However, further research must be conducted exploring whether HBO_2 treatment has special benefit on brain stem infarction or just on acute ventral pons infarction.

Our patient underwent HBO_2 treatment after 2 days of onset, which may not be late for HBO_2 treatment. There is still not a defined “golden time” after onset for treatment, even though some literatures suggest the effectiveness of HBO_2 in brain ischemia would be better within several hours of accident onset.[6,7] There are also some reports indicating that improved oxygenation may reactivate idling neurons even after the event occurred a long time previous to treatment. A literature reported one patient, a 15-year-old girl, who had a near drowning incident at the age of 3, was brought in to undergo 61 HBO_2 treatments.[8] After that, the cognitive, speech and ADL functions were all improved. Another report revealed the restoration of a 7-year unilateral visual field defect in a 58-year-old patient after improved oxygen by extracranial-intracranial arterial anastomosis.[27] This proved HBO_2 treatment could reactivate metabolically lethargic and electrically nonfunctional neurons permanent, even when the event occurred a long time ago.

Contraindication of HBO_2 therapy included pneumothorax, claustrophobia, acute upper respiratory infection or sinusitis, emphysema, and ear complications, Our patient did not have any above contraindications.[28] There is another issue to be considered in that the central nervous system (CNS) is especially sensitive to oxidative stress. Hyperoxia can rapidly disrupt neural function and result in CNS O_2 toxicity.[29] Neurological responses to hyperoxia vary, depending on the oxygen tension in the brain and duration of exposure. For example, the CNS response to hyperoxia can range from moderate, but reversible, changes in neural activity such as dyspnea and abnormal respiration, to violent and reversible seizures at higher levels of oxygen, to irreversible motor deficits and ultimately death at the highest dosages of hyperoxia.[29] In each of these instances, the effects of hyperoxia on the CNS are thought to result from increased production and accumulation of O_2 free radicals and subsequent oxidation of cellular components vital to maintaining normal mechanisms of neuronal exitability.[29] Generally speaking, the dose when applying hyperbaric oxygen treatment in cases of cerebral infarction involved using pressures of 2 to 3 ATA with a length of exposure of at least one hour or longer for a period of 15 to 20 times.[4,15] We applied HBO_2 at pressures of up to 2.0 ATA and with a length of exposure of approximately one hour for each of the 20 treatments. We have used this mode of hyperbaric oxygen therapy for several years and have not encountered any adverse effects.

CONCLUSION

This case not only supports the effectiveness of HBO_2 treatment on ischemic stroke just like other authors’ reports, but also revealed the obvious effectiveness on acute LIS. In clinic, there is no definite indication of effectiveness of HBO_2 on ischemic stroke. However, according to our limited experience and good collateral flows and maintain excellent autoregulation of vertebrobasilar artery system, the overall efficacy of

oxygen delivery may be better in the brain stem region when ischemic infarction occurs. Therefore, we suggest HBO_2 treatment could be used when ischemic stroke happen especially for brain stem infarction such as LIS.

There are methodological limitations in this case report, including that this was only one case, follow up was only for a short period, and that there is a lack of complete understanding with regards to the biologic effect. We cannot exclude the possibility that the recovery resolved spontaneously rather than being due to HBO_2 therapy. Because spontaneous recovery had plateaued within 1 year of onset event,[11] it is important to facilitate functional recovery within this time. Early rehabilitative treatment and intensive nursing is critical.[10] We revealed early HBO_2 treatment could also improve functional recovery in our limited experience. Although the biologic effects still remain to be explained, HBO_2 treatment could be used in conjunction with physical and rehabilitative therapy in the treatment of acute LIS for maximal functional improvement. Further research must be conducted regarding the effectiveness of HBO_2 on the prognosis after acute pontine infarction related LIS.

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